Synthesis and Characterization of Poly(glyceryl glycerol) Block Copolymers

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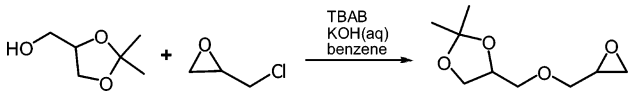
Introduction. Polyglycerol (PG) is an aliphatic polyether exhibiting good chemical stability and inertness under biological conditions. Its biocompatibility is similar to that of poly(ethylene oxide) (PEO)·[1−3] In addition, polyglycerol offers possibilities for versatile further functionalization due to its polyfunctionality and can be obtained as a linear (*l*) or hyperbranched (*hb*) material. Linear diblock copolymers of PEO and PG blocks have been reported by Spassky et al.,[4] who demonstrated the successful polymerization of ethoxyethyl glycidyl ether (EEGE) via a controlled anionic mechanism. The ethoxy ethyl protecting group can be conveniently removed, yielding linear PG with free hydroxyl groups in every repeat unit.[5] Tsvetanov et al. described the synthesis of *l*-poly(glycerol)-*l*-poly(propylene oxide) diblock copolymers.[6] Triblock copolymers consisting of PEO and linear PG were synthesized and studied by Dworak et al.[7] An elegant, recent work by Möller et al.[8] presented linear poly(glycerol)s with orthogonal protecting groups.

Dendritic polymers, both perfectly branched dendrimers[9] and analogous hyperbranched materials,[10] have raised intense interest in the past decade due to their multifunctionality and compact globular structure.[11] Glycerol as a biocompatible structural unit was used both to prepare well-defined dendrimers[12] and as a building unit of hyperbranched polyglycerols obtained by cationic[13] or anionic[14] ring-opening multibranching polymerization (ROMBP) of glycidol. However, linear polyglycerols bearing glycerol side chains have not yet been prepared. In addition, many of the above-mentioned syntheses are based on the use of OsO_4 to transform allyl ether groups into glycerol units. It is desirable to avoid this compound for eventual biomedical application, since it is highly toxic even in low residual amounts in the final polymers.[15]

In numerous papers, the synthesis of linear-dendrimer block copolymers with a linear block as well as a perfect dendrimer block[16] has been described, based on multistep approaches. Only few papers, however, have detailed the preparation of linear-hyperbranched block copolymers.[17] In a previous report, we presented the first synthesis of narrow polydispersity block copolymers based on a linear PEO and a hyperbranched poly(glycerol) (PG) block.[18] Here, we describe the synthesis of novel block copolymers based on PEO and poly(glyceryl glycerol)s (PGG) that can be viewed as a perfect first-generation dendronized polymer based on (poly)glycerol. The synthesis has been realized by two different approaches: in the first route a newly designed monomer for anionic polymerization, DL-1,2-isopropylidene glyceryl glycidyl ether (**1**, IGG), was polymerized onto a prefabricated poly(ethylene oxide) block and converted to well-defined block copolymers, yielding poly(glyceryl glycerol)s after facile deprotection with diluted hydrochloric acid. The IGG structure actually represents an orthogonally protected dimer of glycerol. The synthesis avoids contact with hazardous materials that could cause problems in quantitative removal and is therefore suitable for biomedical application. A second pathway to poly(glyceryl glycerol)s was realized by consecutive polymerization of ethylene oxide and allyl glycidyl ether, relying on a subsequent bishydroxylation step[19] using osmium tetroxide.

Scheme 1. Synthesis of (DL-1,2-Isopropylidene Glyceryl) Glycidyl Ether (1, IGG); TBAB = Tetrabutylammonium Bromide



Results and Discussion. A new bifunctional oxirane monomer for anionic polymerization has been designed that can be readily synthesized under phase transfer conditions, using epichlorohydrine and commercially available DL-1,2-isopropylideneglycerol (solketal) in excellent yields. In different runs 50−80% of pure product was obtained. The resulting monomer (DL-1,2-isopropylidene glyceryl) glycidyl ether (**1**, IGG) was polymerized onto living PEO chains using Cs counterions. The

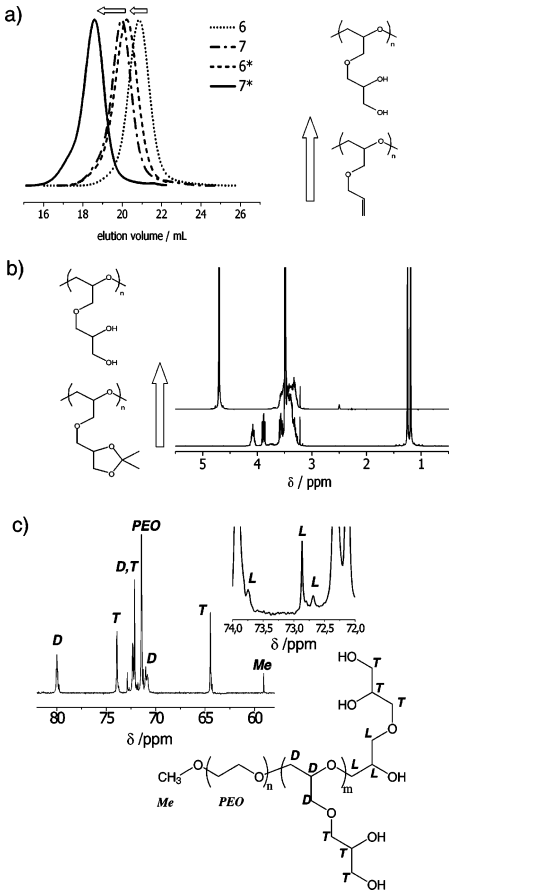


Figure 1. (a) Size exclusion chromatography elugrams of poly(ethylene oxide)-*b*-poly(allyl glycidyl ether) diblock copolymers and their oxidized poly(ethylene oxide)-*b*-poly(glyceryl glycerol) analogues. (b) ^{1}H NMR spectroscopy reveals full deprotection of the poly(glyceryl glycerol) block: (bottom) poly(DL-1,2-isopropylidene glyceryl glycerol) in $CDCl_3$, (top) poly(glyceryl glycerol) in DMSO-d_6. (c) ^{13}C NMR spectrum of poly(ethylene oxide)-*b*-poly(glyceryl glycerol) diblock copolymers, revealing merely dendritic and terminal units. As expected, one single linear segment can be found at the chain end (see inset for enlarged region). D = dendritic, L = linear, T = terminal glycerol unit.

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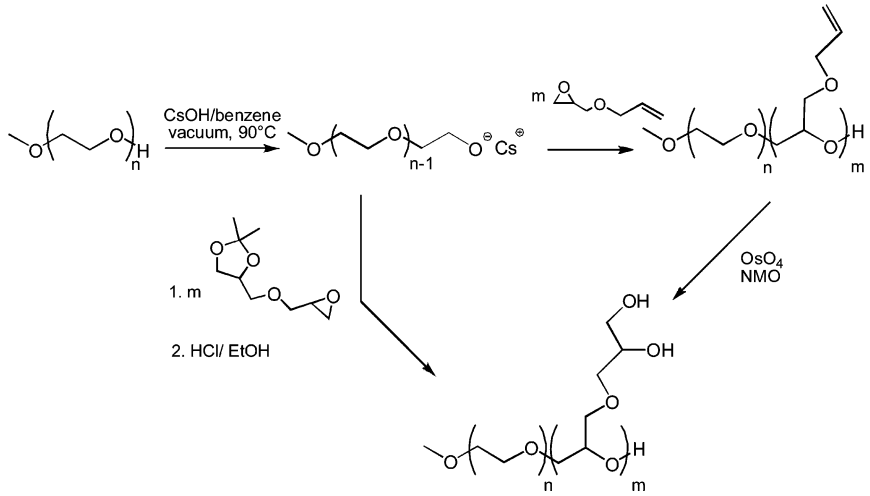
Table 1. Characterization Data of Poly(glyceryl glycerol) Polymers (PGG) Prepared via Both Strategies: Polymerization of (DL-1,2-Isopropylidene Glyceryl) Glycidyl Ether (1, IGG) or Allyl Glycidyl Ether (AGE)[a]

run[b]	sample	DP_n^{theor}	DP_n[c]	DP_n[d]	M_n[d]	DP_n[e]	M_n[e]	PDI[e]
1	$PEO_{45}-PIGG_x$	10	11	11	4000	6	3100	1.15
1*	$PEO_{45}-PGG_x$	10	10	13	4400	9	3300	1.18
2	$PEO_{114}-PIGG_x$	25	26	25	9800	9	6800	1.05
2*	$PEO_{114}-PGG_x$	25	22	42	11300	19	7800	1.09
3	$PEO_{114}-PIGG_x$	80	25	25	9800	10	7000	1.08
4	$PIGG_x$	25	11	10	2400	6	1400	1.13
4*	PGG_x	25	10	12	1800	7	1100	1.18
5	$PAGE_x$	30	27	27	3200	21	2400	1.08
5*	PGG_x	30	27	48	7000	30	4400	1.08
6	$PEO_{17}-PAGE_x$	40	31	31	4300	21	3200	1.11
6*	$PEO_{17}-PGG_x$	40	30	57	9300	36	6200	1.13
7	$PEO_{45}-PAGE_x$	20	23	23	4600	12	3400	1.09
7*	$PEO_{45}-PGG_x$	20	20	33	7000	16	4400	1.13

[a] M_n = number-average of the molecular weight distribution determined via size exclusion chromatography (SEC), DP_n = degree of polymerization (here for PIGG, PAGE, or PGG blocks), and PDI = polydispersity index. [b] Note: samples denoted with a "*" were synthesized from the corresponding run without "*". [c] Determined via end-group analysis from ^{1}H NMR spectroscopy data. [d] Determined via size exclusion chromatography (refractive index detection) using *N*,*N*-dimethylformamide (DMF) as an eluent (polystyrene standards). [e] Determined via size exclusion chromatography (refractive index detection) using *N*,*N*-dimethylformamide (DMF) as an eluent (poly(ethylene oxide) standards).

Scheme 2. Two Different Strategies Established for the Synthesis of Poly(glyceryl glycerol)s; NMO = *N*-Methylmorpholine *N*-Oxide



preparation of the new epoxide monomer is shown in Scheme 1. IGG exhibits orthogonal behavior and is in fact a protected dimer of glycerol. The epoxide group acts as the polymerizable, latent glycerol moiety, while the acetal protecting group is very stable during anionic polymerization and can be conveniently cleaved subsequent to polymerization to generate the side-chain glycerol moiety. Hydrolytic cleavage of the acetal protecting group after polymerization can be performed directly in the polymerization vessel without additional workup steps, using diluted HCl.

The polymerization of **1** with cesium counterions can be controlled. Size exclusion chromatography (SEC) revealed a narrow molecular weight distribution, and NMR spectroscopy confirmed full conversion and the expected signals for the acetal protecting group. Deprotection of the pending glycerol units via acetal cleavage was complete within several minutes. The degree of deprotection of the polymer was monitored by both IR and NMR spectroscopy. The resulting polymer bears two additional hydroxyl groups in every PGG repeat unit. Regarding the degree of branching for these materials, in fact a linear polyglycerol "pseudo-dendrimer" structure is obtained, since only one linear group is present, while the number of dendritic and terminal groups is equal to the degree of polymerization. As expected, ^{13}C NMR characterization of PEO−PGG diblock copolymers confirms the presence of merely dendritic and terminal units. Only one linear segment can be found at the chain end. Consequently, inverse-gated ^{13}C NMR spectroscopy confirms a degree of branching of close to unity (cf. Figure 1).

It is a drawback of this polymerization that the degree of polymerization appears to be limited to 25−40 units using this polymerization technique (with cesium as counterion); a similar result concerning the limitation of the degree of polymerization was reported by Tsvetanov et al. for the synthesis of PEEGE with ~100 repeat units.[6] Only oligomers could be prepared by homopolymerization of **1** under these conditions. We assume this may be due to deprotonation of the monomer during the reaction, as reported in the literature for other oxirane monomers,[20] limiting the degree of polymerization. However, **1** can be polymerized to a second block onto a living chain in quantitative yields with up to 40 repeating units. We tentatively explain this by a shielding effect due to the existing polymer block (cf. Table 1). All polymerizations resulted in quantitative yields and full conversion, when the degree of polymerization (DP_n) of PGG was adjusted to this limit. Experiments 3 and 4 (Table 1) show incomplete polymerization; nevertheless, the resulting polymers exhibit narrow molecular weight distributions. The reason for the limitation of the DP_n is presently under investigation and not yet clear. A second approach for the synthesis of PGG homopolymers and block copolymers was developed, using a three-step synthesis. In the first step, the preparation of PEO and subsequent polymerization of the commercially available monomer allyl glycidyl ether (AGE)

gave PEO-*b*-PAGE precursor polymers with narrow polydispersities ($M_w/M_n < 1.10$) and good control over molecular weight, even with extended blocks of the functional monomer.

In a third step the pendant allyl groups were oxidized using catalytic amounts of osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMO)[21] in the same manner, as it has been reported for the end groups of linear and dendritic poly(ethylene oxide) chains by Haag et al.[12] and further developed in an elegant synthesis for dendritic PEOs by Gnanou et al.[22] to transform allyl ether units into etherified glycerol structures.

For all samples with PAGE block after bishydroxylation a PGG polymer block was obtained in excellent yield and full conversion, as demonstrated by both IR and NMR spectroscopy. Table 1 summarizes characterization data for all polymers prepared in this study, varying the molecular weight of both PEO and PGG segments. Unfortunately, molecular weight determination via ^{1}H NMR spectroscopy is error-prone due to the lack of a well-separated end-group signal. A forthcoming paper will present a combination of other methods for quantitative determination of the degree of polymerization. For practical purposes it may be mentioned that conventional SEC is suitable for molecular weight determination; the PIGG and the PAGE containing polymers give the expected values for the molecular weight using polystyrene standards, while the PGG series of polymers leads to reasonable results only with PEO standards in *N*,*N*-dimethylformamide (DMF) as an eluent.

Conclusion. This Communication presents the first synthesis of poly(glyceryl glycerols) (PGG) by two different synthetic strategies, introducing a new solketyl glycidyl ether monomer IGG **(1)**. The second strategy relies on the polymerization of allyl glycidyl ether and subsequent bishydroxylation. Both strategies possess their respective advantages. Most important, the first strategy avoids the use of the toxic osmium tetroxide; thus, the resulting polymers are suitable for biomedical applications, while the second pathway can be used to achieve higher degrees of polymerization for PGG. However, it is a drawback of the latter method that complete removal of residual osmium traces usually performed by dialysis from the polyfunctional polymer may be difficult.

Because of their multifunctionality, these PEO-analogous functional polymers can be used for a variety of further applications, e.g., as macroinitiators for the anionic ring-opening multibranching polymerization (ROMBP) of glycidol, affording well-defined linear-hyperbranched *l*-poly(ethylene oxide)-*hb*-poly(glycerol) block copolymers. A forthcoming full paper will deal with other polymerization pathways for the novel (DL-1,2-isopropylidene glyceryl) glycidyl ether monomer to well-defined homopolymers and block copolymers and to more complex polyether structures.

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Supporting Information Available: Syntheses and detailed NMR characterization of **1** and additional spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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